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(54) Title: THROMBIN OR FACTOR Xa INHIBITORS

(57) Abstract: This invention relates generally to heteroaryl-phenyl substituted compounds that are inhibitors of trypsin-like serine protease enzymes, especially factor Xa or thrombin, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

TITLE

Thrombin or Factor Xa Inhibitors

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FIELD OF THE INVENTION

This invention relates generally to heteroaryl-phenyl substituted compounds that are inhibitors of trypsin-like serine protease enzymes, especially factor Xa or thrombin, pharmaceutical compositions containing the same, and methods 10 of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

BACKGROUND OF THE INVENTION

Activated factor Xa, whose major practical role is the 15 generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to 20 generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin, inhibition of factor Xa may be more efficient than 25 inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor Xa, thrombin, or both are needed as potentially valuable therapeutic agents for the treatment of 30 thromboembolic disorders. It is thus desirable to discover new factor Xa, thrombin, or both inhibitors.

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel heteroaryl-phenyl substituted compounds that are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

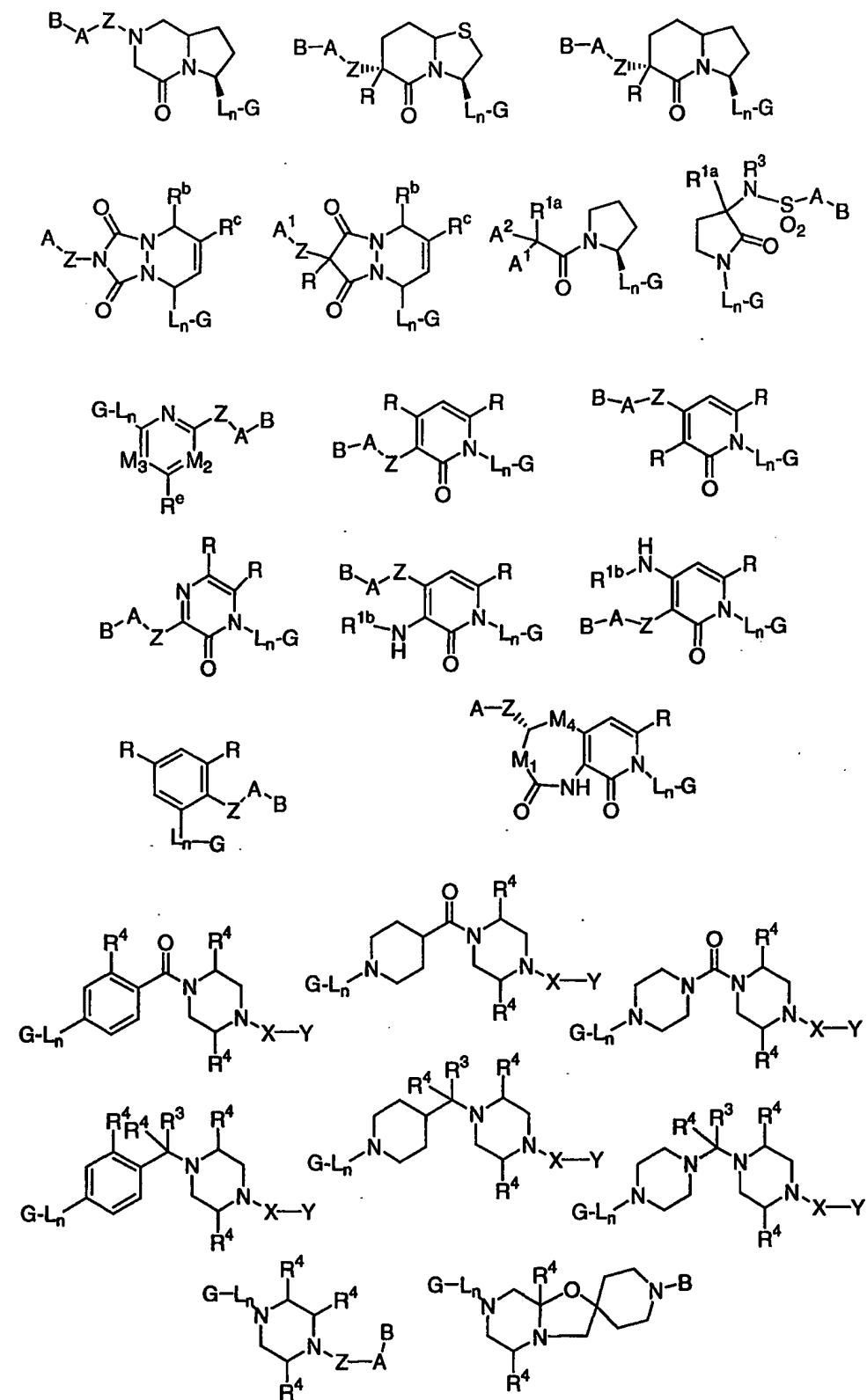
It is another object of the present invention to provide a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

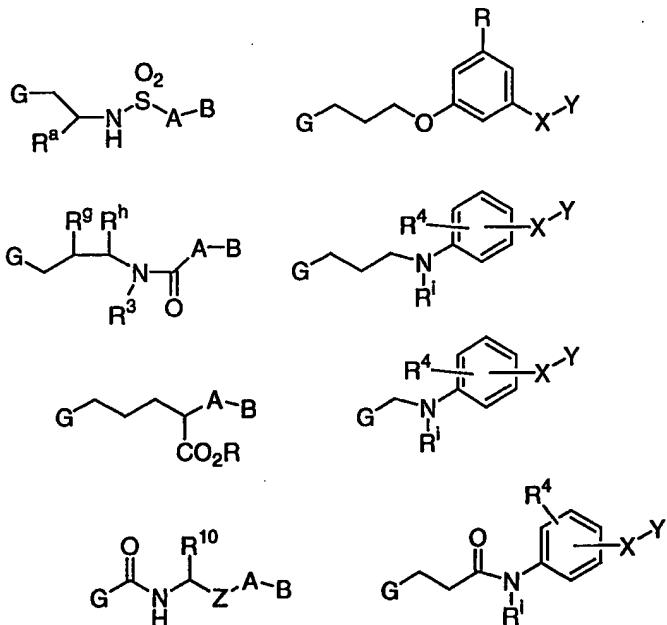
It is another object of the present invention to provide novel compounds for use in therapy.

It is another object of the present invention to provide the use of novel compounds for the manufacture of a medicament for the treatment of thrombosis or a disease mediated by factor Xa.

25 DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in an embodiment, the present invention provides a novel compound selected from the group:

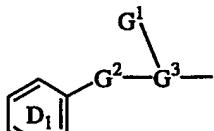




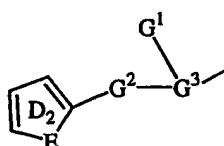
or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

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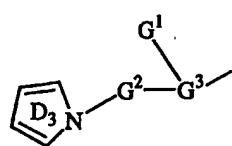
G is selected from formulas Ia-Ic:



Ia



Ib



Ic

10

ring D₁ is selected from pyridine, pyrazine, pyridazine, and pyrimidine and is substituted with 1 D_{1a} and 0-1 D_{1b};

ring D₂ is a 5-membered heteroaromatic ring system

15 comprising E, carbon atoms, and 0-3 N atoms, wherein E is selected from O, S, and N-D_{1c} and ring D₂ is substituted with 1 D_{1a} and 0-1 D_{1b};

ring D₃ is a 5-membered heteroaromatic ring system comprising carbon atoms and from 0-3 additional N atoms and ring D₃ is substituted with 1 D_{1a} and 0-1 D_{1b};

5 G¹ is selected from H, C₁₋₄ alkyl, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, CN, C(=NR⁸)NR⁷R⁹, NHC(=NR⁸)NR⁷R⁹, NR⁸CH(=NR⁷), NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

10 D_{1a} is selected from H, C₁₋₄ alkyl, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, CN, C(=NR⁸)NR⁷R⁹, NHC(=NR⁸)NR⁷R⁹, NR⁸CH(=NR⁷), NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

15 D_{1b} is selected from H, C₁₋₄ alkyl, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, CN, C(=NR⁸)NR⁷R⁹, NHC(=NR⁸)NR⁷R⁹, NR⁸CH(=NR⁷), NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

20 D_{1c} is selected from H, C₁₋₄ alkyl, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

25 D_{1c} is selected from H, C₁₋₄ alkyl, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

30 D_{1c} is selected from H, C₁₋₄ alkyl, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

5 G^2 is absent or is selected from CH_2 , $C(O)$, O , NR^3 , $S(O)_p$,
 CH_2CH_2 , $C(O)CH_2$, $CH_2C(O)$, OCH_2 , CH_2O , NR^3CH_2 , CH_2NR^3 ,
 $S(O)_pCH_2$, $CH_2S(O)_p$, $CH_2CH_2CH_2$, $C(O)CH_2CH_2$, $CH_2C(O)CH_2$,
 $CH_2CH_2C(O)$, OCH_2CH_2 , CH_2OCH_2 , CH_2CH_2O , $NR^3CH_2CH_2$, $CH_2NR^3CH_2$,
 $CH_2CH_2NR^3$, $S(O)_pCH_2CH_2$, $CH_2S(O)_pCH_2$, and $CH_2CH_2S(O)_p$;

10 G^3 is phenyl, naphthyl, or a 5-10 membered heteroaryl
 consisting of carbon atoms and from 1-3 heteroatoms
 selected from N, O, and S;

15 L_n is a linker which is absent or is selected from O, S,
 $S(O)_2$, CH_2 , $*NHC(O)$, $*C(O)NH$, $*S(O)_2NH$, $*NHS(O)_2$,
 $*CH_2NHC(O)$, $*CH(R^a)NHC(O)$, $*CH_2NHC(O)CH_2$, and
 $*CH(R^a)NHC(O)CH_2$, provided that L_n and M do not form an
 O-N or S-N bond and the * indicates where L_n is bonded
 to G;

20 M^1 is absent or is selected from CHR , O , and NR^3 ;
 M^2 is N or CR^f ;

25 M^3 is N or CR^d ;
 provided that only one of M^2 and M^3 is N;

M^4 is selected from NR^3 , CR^f , and $C(O)$;

30 R^a is selected from $C(O)C(O)OR^3$, $C(O)C(O)NR^2R^{2a}$, and $C(O)-A$;

R^b is selected from H, R, phenyl, C₁₋₁₀ alkyl, and C₂₋₅ alkenyl;

R^c is selected from H and C₁₋₆ alkyl;

5

alternatively, R^b and R^c together are -(CH₂)₄-;

R^d is selected from H, F, and Cl;

10 R^e is selected from H, N(CH₃)(CH₂CO₂H) and S-(5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴);

15 alternatively, R^d and R^e combine to form -NR³-C(O)-C(R^{1g}R³)-NR³- or -N=CR²-NR³-;

R^f is selected from H, F, and Cl;

20 alternatively, R^e and R^f combine to form -NR³-C(R^{1g}R³)-C(O)-NR³- or -NR³-CR²=N-;

R^g is selected from H, CH₂OR³, CH₂C(O)OR³, C₁₋₄ alkyl, C(O)NH₂, and NH₂;

25

R^h is selected from H, CH₂-phenyl, CH₂CH₂-phenyl, and CH=CH-phenyl;

30 Rⁱ is selected from SO₂CH₂C(O)OR³, C(O)CH₂C(O)OR³, and C(O)OR³;

R is selected from H, Cl, F, Br, I, $(CH_2)_tOR^3$, C_{1-4} alkyl, benzyl, OCF_3 , CF_3 , $C(O)NR^7R^8$, $(CH_2)_tNR^2SO_2-C_{1-4}$ alkyl, and $(CR^8R^9)_tNR^7R^8$;

5 Z is selected from a $(CR^8R^9)_{1-4}$, $(CR^8R^9)_rO(CR^8R^9)_r$,
 $(CR^8R^9)_rNR^3(CR^8R^9)_r$, $(CR^8R^9)_rNR^3C(=CHR^8)(CR^8R^9)_r$,
 $(CR^8R^9)_rC(O)(CR^8R^9)_r$, $(CR^8R^9)_rC(O)O(CR^8R^9)_r$,
 $(CR^8R^9)_rOC(O)(CR^8R^9)_r$, $(CR^8R^9)_rC(O)NR^3(CR^8R^9)_r$,
 $(CR^8R^9)_rNR^3C(O)(CR^8R^9)_r$, $(CR^8R^9)_rOC(O)O(CR^8R^9)_r$,
10 $(CH_2)_rOC(O)NR^3(CR^8R^9)_r$, $(CR^8R^9)_rNR^3C(O)O(CR^8R^9)_r$,
 $(CH_2)_rNR^3C(O)NR^3(CR^8R^9)_r$, $(CR^8R^9)_rS(O)_p(CR^8R^9)_r$,
 $(CR^8R^9)_rS(O)_2(CH=CH)$, $(CCR^8R^9)_rSO_2NR^3(CR^8R^9)_r$,
 $(CR^8R^9)_rNR^3SO_2(CR^8R^9)_r$, and $(CR^8R^9)_rNR^3SO_2NR^3(CR^8R^9)_r$,
provided that Z does not form a N-N, N-O, N-S, NCH_2N ,
15 NCH_2O , or NCH_2S bond with the groups to which Z is
attached;

R^{1a} is selected from H, $-(CH_2)_r-R^{1b}$, $-CH=CH-R^{1b}$, NCH_2R^{1c} ,
 OCH_2R^{1c} , SCH_2R^{1c} , $NH(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$,
20 $S(CH_2)_2(CH_2)_tR^{1b}$, $S(O)_p(CH_2)_tR^{1a}$, $O(CH_2)_tR^{1a}$, $NR^3(CH_2)_tR^{1a}$,
 $OC(O)NR^3(CH_2)_tR^{1a}$, $NR^3C(O)NR^3(CH_2)_tR^{1a}$, $NR^3C(O)O(CH_2)_tR^{1a}$, and
 $NR^3C(O)(CH_2)_tR^{1a}$, provided that R^{1a} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

25 R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a} , $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2a}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $C(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^{2a}R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6}

carbocycle substituted with 0-2 R^{4a}, and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S(O), substituted with 0-2 R^{4a}, provided that R^{1b} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

5 R^{1c} is selected from H, CH(CH₂OR²)₂, C(O)R^{2c}, C(O)NR²R^{2a},

10 S(O)R^{2b}, S(O)₂R^{2b}, and SO₂NR²R^{2a};

10

R^{1d} is selected from C₃₋₁₃ carbocycle substituted with 0-2 R^{4a}, and 5-13 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S(O), substituted with 0-2 R^{4a}, provided that R^{1d} forms other than an N-N, N-S, or N-O bond;

15

R^{1g} is selected from H, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted with A;

20

R², at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

25

R^{2a}, at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl, benzyl, C₃₋₆ cycloalkylmethyl substituted with 0-2 R^{4b}, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4

30

heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

5 R^{2b}, at each occurrence, is selected from CF₃, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

10 R^{2c}, at each occurrence, is selected from CF₃, OH, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with
15 0-2 R^{4b};

alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring
20 substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

25 R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

30 R^{3b}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3c} , at each occurrence, is selected from C_{1-4} alkyl, and phenyl;

5 R^{3d} , at each occurrence, is selected from H, C_{1-4} alkyl, C_{1-4} alkyl-phenyl, and $C(=O)R^{3c}$;

A is selected from:

10 C_{3-10} carbocyclic residue substituted with 0-2 R^4 , and 5-12 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4 ;

A^1 is H or A;

15 alternatively, A and A^1 and the carbon to which they are attached combine to form fluorene;

A^2 is selected from H, A, and CHA^3A^4 ;

20 A^3 is selected from H, A, C_{1-4} alkyl, and $-(CH_2)_zNR^2R^{2a}$;

A^4 is H or A;

25 B is selected from: H, Y, and X-Y, provided that Z and B are attached to different atoms on A;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$,
-C(=NR^{1c})-, $-CR^2(NR^{1c}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$,
30 $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S-$, $-S(O)-$, $-S(O)_2-$,
 $-SCR^2R^{2a}-$, $-S(O)CR^2R^{2a}-$, $-S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S-$,

-CR²R^{2a}S(O)-, -CR²R^{2a}S(O)₂-, -S(O)₂NR²-, -NR²S(O)₂-,
 -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-,
 -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-,
 -CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-,
 5 -NR²C(O)NR²-, -NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O,
 -CR²R^{2a}O-, and -OCR²R^{2a}-;

Y is selected from:

C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and
 10 5-12 membered heterocyclic system containing from 1-4
 heteroatoms selected from the group consisting of N, O, and
 S substituted with 0-2 R^{4a};

alternatively, Z-A-B combine to form S-C₁₋₆ alkyl;

15 R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
 (CH₂)_rF, (CH₂)_rCl, (CH₂)_rBr, (CH₂)_rI, C₁₋₄ alkyl,
 (CH₂)_rCN, (CH₂)_rNO₂, (CH₂)_rNR²R^{2a}, C(O)R^{2c}, NR²C(O)R^{2b},
 C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)NR²R^{2a},
 20 C(=NS(O)₂R⁵)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, C(O)NHC(=NR²)NR²R^{2a},
 SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵,
 S(O)_pR⁵, (CF₂)_rCF₃, (CH₂)_r-CF₃, NCH₂R^{1c}, OCH₂R^{1c}, SCH₂R^{1c},
 N(CH₂)₂(CH₂)_tR^{1b}, O(CH₂)₂(CH₂)_tR^{1b}, S(CH₂)₂(CH₂)_tR^{1b}, 5-6
 membered carbocycle substituted with 0-1 R⁵, and 5-6
 25 membered heterocycle consisting of: carbon atoms and
 1-4 heteroatoms selected from the group consisting of
 N, O, and S(O), substituted with 0-1 R⁵;

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
 30 (CF₂)_rCF₃, (CH₂)_r-CF₃, (CH₂)_r-F, (CH₂)_r-Br, (CH₂)_r-Cl,

C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^2R^{2a}$,
 $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $(CH_2)_rN=CHOR^3$,
 $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$,
 $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$
5 alkyl, $NR^2SO_2R^5$, $C(O)NHSO_2-C_{1-4}$ alkyl, $S(O)_pR^5$, 5-6
 membered carbocycle substituted with 0-1 R^5 , and 5-6
 membered heterocycle consisting of: carbon atoms and
 1-4 heteroatoms selected from the group consisting of
 N, O, and $S(O)$, substituted with 0-1 R^5 ;
10 R^{4b} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$,
 $(CH_2)_r-F$, $(CH_2)_r-Cl$, $(CH_2)_r-Br$, $(CH_2)_r-I$, C_{1-4} alkyl,
 $(CH_2)_r-CN$, $(CH_2)_r-NO_2$, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$,
 $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$,
15 $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$,
 $NR^3SO_2-C_{1-4}$ alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl, $S(O)_pCF_3$,
 $S(O)_p-C_{1-4}$ alkyl, $S(O)_p$ -phenyl, $(CH_2)_rCF_3$, and $(CF_2)_rCF_3$;

 R^5 , at each occurrence, is selected from H, C_{1-6} alkyl, =O,
20 $(CH_2)_rOR^3$, F, Cl, Br, I, -CN, NO_2 , $(CH_2)_rNR^3R^{3a}$,
 $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$,
 $NR^3C(O)NR^3R^{3a}$, $CH(=NOR^{3d})$, $C(=NR^3)NR^3R^{3a}$,
 $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, $NR^3SO_2-C_{1-4}$
 alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl, $S(O)_pCF_3$, $S(O)_p-C_{1-4}$
25 alkyl, $S(O)_p$ -phenyl, $(CF_2)_rCF_3$, phenyl substituted with
 0-2 R^6 , naphthyl substituted with 0-2 R^6 , and benzyl
 substituted with 0-2 R^6 ;

R⁶, at each occurrence, is selected from H, OH, (CH₂)_rOR², halo, C₁₋₄ alkyl, CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2b}, NR²C(O)R^{2b}, NR²C(O)NR²R^{2a}, C(=NH)NH₂, NHC(=NH)NH₂, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, and NR²SO₂C₁₋₄ alkyl;

5

R⁷, at each occurrence, is selected from H, OH, C₁₋₄ alkoxy carbonyl, C₆₋₁₀ aryloxy, C₆₋₁₀ aryloxycarbonyl, C₆₋₁₀ arylmethyl carbonyl, C₁₋₄ alkyl carbonyloxy C₁₋₄ alkoxy carbonyl, C₆₋₁₀ aryl carbonyloxy C₁₋₄ alkoxy carbonyl, C₁₋₆ alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C₁₋₄ alkoxy carbonyl;

10

R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl, and (CH₂)_n-phenyl;

15

alternatively, R⁷ and R⁸, when attached to the same nitrogen, combine to form a 5-6 membered heterocyclic ring consisting of carbon atoms and 0-2 additional heteroatoms selected from the group consisting of N, O, and S(O);

20

R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and (CH₂)_n-phenyl;

25

R¹⁰ is selected from H, phenyl substituted with 0-2 R^{4a}, and naphthyl substituted with 0-2 R^{4a};

n, at each occurrence, is selected from 0, 1, 2, and 3;

30

m, at each occurrence, is selected from 0, 1, and 2;

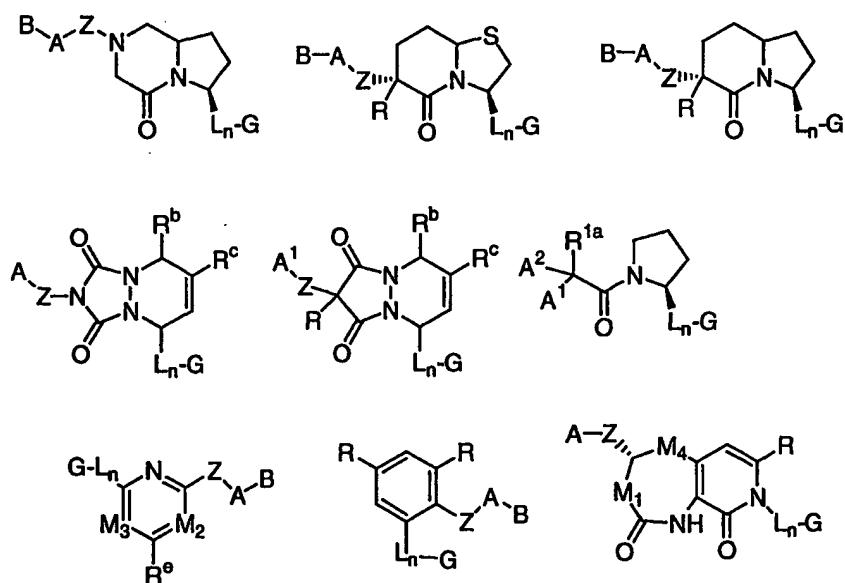
p, at each occurrence, is selected from 0, 1, and 2;

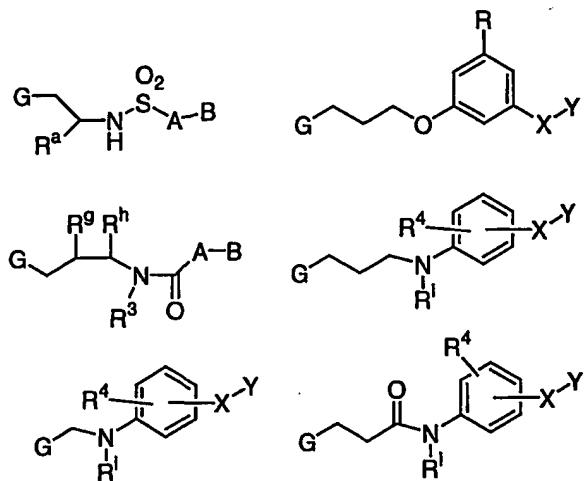
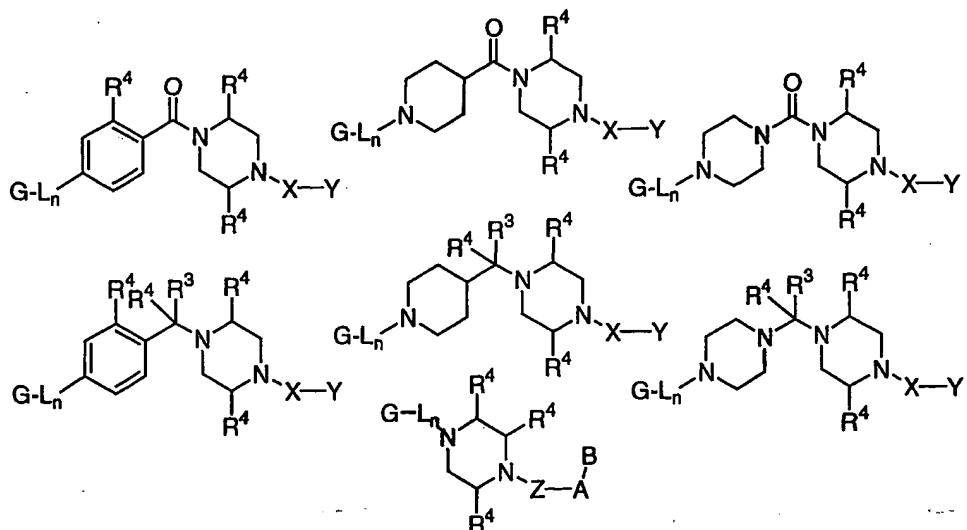
r, at each occurrence, is selected from 0, 1, 2, and 3;

5 s, at each occurrence, is selected from 0, 1, and 2; and,

t, at each occurrence, is selected from 0, 1, 2, and 3.

10 [2] Thus, in another embodiment, the present invention provides a novel compound selected from the group:

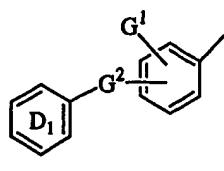




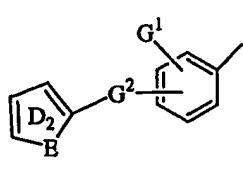
5 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

G is selected from formulas Ia₁-Ic₁:

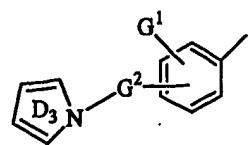
10



Ia₁



Ib₁



Ic₁

ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-D_{1c} and ring D₂ is 5 substituted with 1 D_{1a} and 0-1 D_{1b};

ring D₃ is a 5-membered heteroaromatic ring system comprising carbon atoms and from 0-3 additional N atoms and ring D₃ is substituted with 1 D_{1a} and 0-1 D_{1b};

10 G¹ is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

15 D_{1a} is selected from H, OH, SH, C₁₋₃ alkoxy, C₁₋₃ thioalkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

20 D_{1b} is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

25 D_{1c} is selected from H, C₁₋₄ alkyl, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

30

Z is selected from a bond, CH_2O , OCH_2 , CH_2NH , NHCH_2 ,
 $\text{NHC}(\text{=CH}_2)$, $\text{C}(\text{O})$, $\text{CH}_2\text{C}(\text{O})$, $\text{C}(\text{O})\text{CH}_2$, $\text{NHC}(\text{O})$, $\text{C}(\text{O})\text{NH}$,
 $\text{NHC}(\text{O})\text{NH}$, $\text{CH}_2\text{S}(\text{O})_2$, $\text{S}(\text{O})_2(\text{CH}_2)$, SO_2NH , and NHSO_2 ,
provided that Z does not form a N-N, N-O, NCH_2N , or
5 NCH_2O bond with ring M or group A;

A is selected from one of the following carbocyclic and
heterocyclic systems which are substituted with 0-2 R^4 ;
phenyl, piperidinyl, piperazinyl, pyridyl,
10 pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,
isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,
thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,
1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,
15 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,
1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,
1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,
benzothiophenyl, indolyl, benzimidazolyl,
20 benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,
benzisothiazolyl, and isoindazolyl;

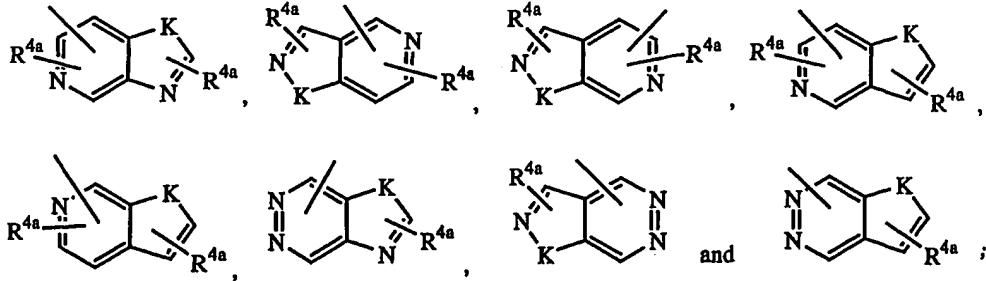
X is selected from C_{1-4} alkylene, $-\text{C}(\text{O})-$, $-\text{C}(\text{=NR})-$,
 $-\text{CR}^2(\text{NR}^2\text{R}^{2a})-$, $-\text{C}(\text{O})\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{C}(\text{O})$, $-\text{C}(\text{O})\text{NR}^2-$,
25 $-\text{NR}^2\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^2\text{CR}^2\text{R}^{2a}-$, $-\text{NR}^2\text{C}(\text{O})\text{CR}^2\text{R}^{2a}-$,
 $-\text{CR}^2\text{R}^{2a}\text{C}(\text{O})\text{NR}^2-$, $-\text{CR}^2\text{R}^{2a}\text{NR}^2\text{C}(\text{O})-$, $-\text{NR}^2\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2-$,
 $-\text{NR}^2\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{NR}^2-$, O, $-\text{CR}^2\text{R}^{2a}\text{O}-$, and $-\text{OCR}^2\text{R}^{2a}-$;

alternatively, Y is selected from one of the following
30 carbocyclic and heterocyclic systems which are
substituted with 0-2 R^{4a} ;

cyclopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, 5 isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 10 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

15

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



20 K is selected from O, S, NH, and N;

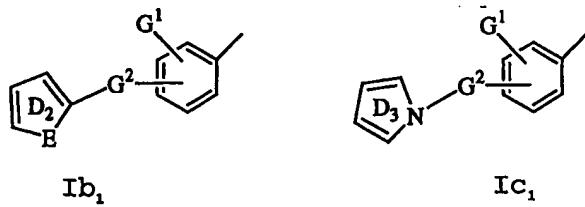
R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, CN, NO₂, (CH₂)_rNR²R^{2a}, C(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)NR²R^{2a}, 25 SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵, S(O)_pR⁵, CF₃, NCH₂R^{1c}, OCH₂R^{1c}, SCH₂R^{1c}, N(CH₂)₂(CH₂)_tR^{1b},

$O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, 5-6 membered carbocycle substituted with 0-1 R^5 , and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O), substituted with 0-1 R^5 ; and,

R^{4a} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, CF_3 , F, Br, Cl, C₁₋₄ alkyl, CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $C(O)NHSO_2-C_{1-4}$ alkyl, $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1 R^5 , and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O), substituted with 0-1 R^5 .

[3] Thus, in another embodiment, the present invention provides a novel compound, wherein:

20 G is selected from formulas Ib₁ and Ic₁:



25 ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-D_{1c} and ring D₂ is substituted with 1 D_{1a} and 0-1 D_{1b};

G^1 is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

5

D_{1a} is selected from H, OH, SH, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

10 D_{1b} is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

15 D_{1c} is selected from H, C₁₋₄ alkyl, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

20 phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran, benzothiophuran, indole, benzimidazole, benzimidazolone, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole;

25

30

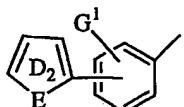
5 Z is selected from a bond, CH₂O, OCH₂, NH, CH₂NH, NHCH₂,
CH₂C(O), C(O)CH₂, C(O)NH, NHC(O), CH₂S(O)₂, S(O)₂(CH₂),
SO₂NH, and NHSO₂, provided that Z does not form a N-N,
N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond with either group
to which it is attached;

10 R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F,
Cl, Br, I, C₁₋₄ alkyl, CN, NO₂, (CH₂)_rNR²R^{2a}, C(O)R^{2c},
NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)NR²R^{2a},
SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵,
S(O)_pR⁵, CF₃, 5-6 membered carbocycle substituted with
0-1 R⁵, and 5-6 membered heterocycle consisting of:
15 carbon atoms and 1-4 heteroatoms selected from the
group consisting of N, O, and S(O), substituted with 0-1
R⁵; and,

20 R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
CF₃, F, Br, Cl, C₁₋₄ alkyl, CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a},
C(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, C(O)NHSO₂-C₁₋₄ alkyl, S(O)_pR⁵,
5-6 membered carbocycle substituted with 0-1 R⁵, and 5-6
membered heterocycle consisting of: carbon atoms and
1-4 heteroatoms selected from the group consisting of
25 N, O, and S(O), substituted with 0-1 R⁵.

30 [4] In a preferred embodiment, the present invention
provides a novel compound, wherein:

30 G is of formula Ib₂:

Ib₂

5 ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-D_{1c} and ring D₂ is substituted with 1 D_{1a} and 0-1 D_{1b};

10 G¹ is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

15 D_{1a} is selected from H, OH, SH, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

20 D_{1b} is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

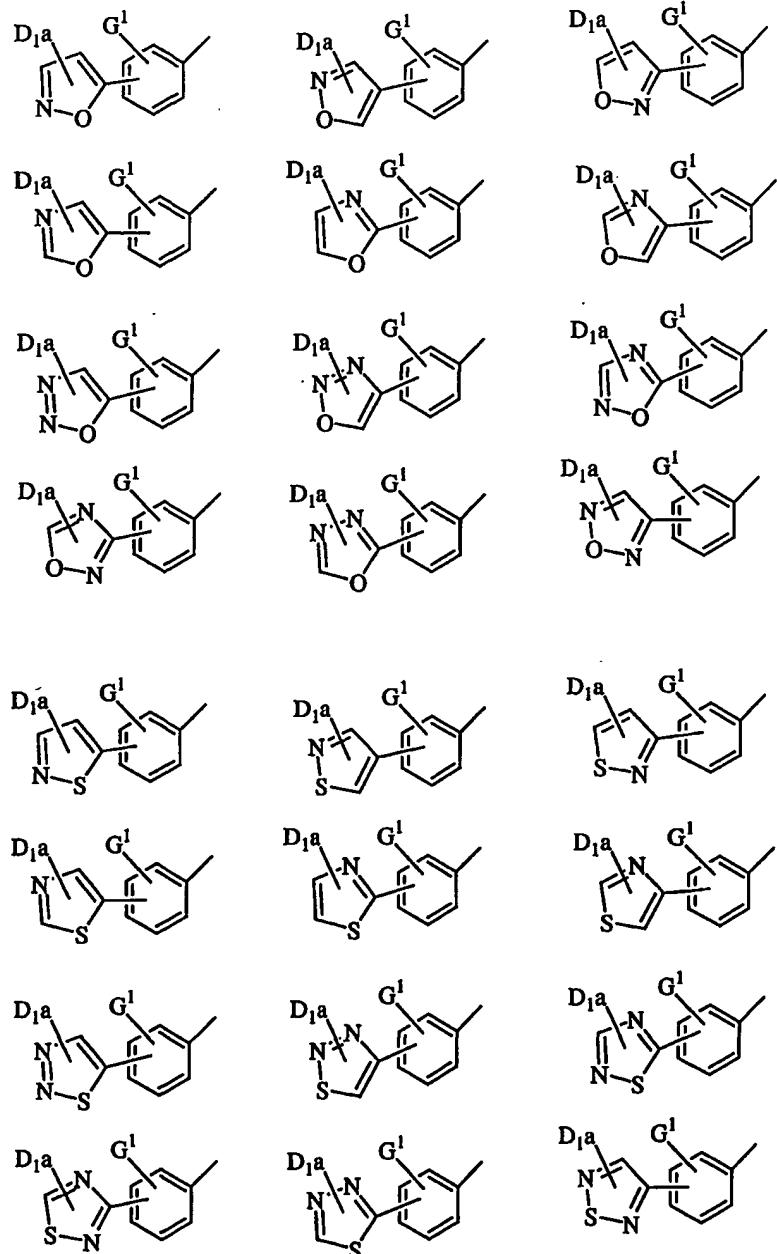
25 D_{1c} is selected from H, C₁₋₄ alkyl, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂; and,

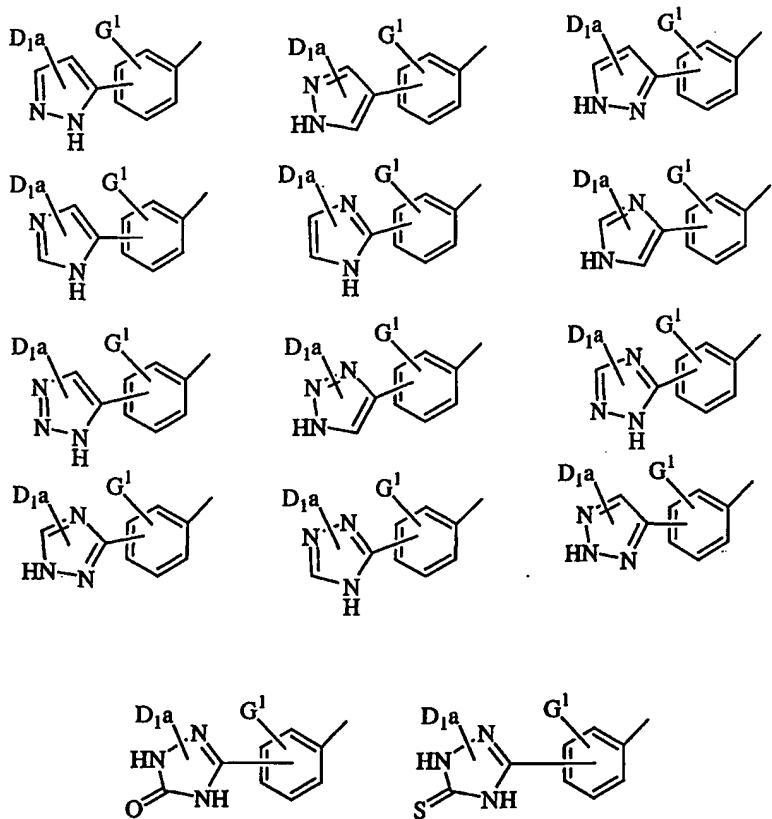
 R is selected from H, Cl, F, Br, I, (CH₂)_tOR³, C₁₋₄ alkyl, OCF₃, CF₃, C(O)NR⁷R⁸, (CR⁸R⁹)_tNR⁷R⁸ and (CH₂)_tNR²SO₂-CH₃.

[5] In a more preferred embodiment, the present invention provides a novel compound, wherein:

G is selected from the group:

5





5 Z is selected from $\text{C}(\text{O})\text{CH}_2$ and $\text{C}(\text{O})\text{NH}$, provided that Z does not form a N-N bond with group A;

A is selected from phenyl, piperidinyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4 ; and,

10

B is selected from phenyl, pyrrolidino, N-pyrrolidino-carbonyl, morpholino, N-morpholino-carbonyl, 1,2,3-triazolyl, imidazolyl, and benzimidazolyl, and is substituted with 0-1 R^{4a} ;

15

R^2 , at each occurrence, is selected from H, CH_3 , CH_2CH_3 , cyclopropylmethyl, cyclobutyl, and cyclopentyl;

R^{2a} , at each occurrence, is selected from H, CH_3 , and CH_2CH_3 ;

alternatively, R^2 and R^{2a} , together with the atom to which
they are attached, combine to form pyrrolidine

5 substituted with 0-2 R^{4b} or piperidine substituted with
0-2 R^{4b} ;

R^4 , at each occurrence, is selected from OH, OR^2 , $(CH_2)OR^2$,

$(CH_2)_2OR^2$, F, Br, Cl, I, C_{1-4} alkyl, NR^2R^{2a} , $(CH_2)NR^2R^{2a}$,

10 $(CH_2)_2NR^2R^{2a}$, CF_3 , and $(CF_2)CF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3 , OR^2 , $(CH_2)OR^2$,
 $(CH_2)_2OR^2$, NR^2R^{2a} , $(CH_2)NR^2R^{2a}$, $(CH_2)_2NR^2R^{2a}$, SR^5 , $S(O)R^5$,
 $S(O)_2R^5$, $SO_2NR^2R^{2a}$, and 1- CF_3 -tetrazol-2-yl;

15

R^{4b} , at each occurrence, is selected from H, CH_3 , and OH;

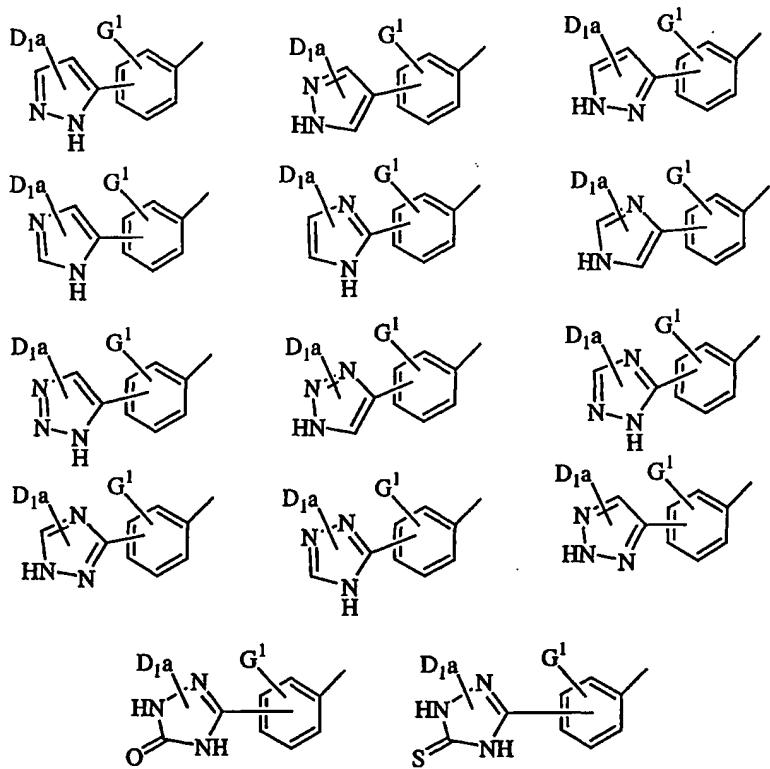
R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl,
phenyl, and benzyl; and,

20

r , at each occurrence, is selected from 0, 1, and 2.

[6] In an even further preferred embodiment, the present
25 invention provides a novel compound, wherein:

G is selected from:



A is selected from the group: phenyl, piperidinyl, 2-

5 pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

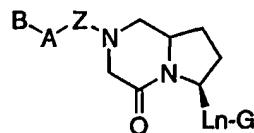
B is selected from the group: 2-(aminosulfonyl)phenyl, 2-

10 (methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N-methylaminomethyl)phenyl, 2-(N-ethyl-N-methylaminomethyl)phenyl, 2-(N-aminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(methylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-

(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.

5

[7] In another even more preferred embodiment, the present invention provides a compound of formula:



10

L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$, the * indicates where L_n is bonded to G;

R^a is $C(O)C(O)OR^3$;

15

Z is selected from a C_{1-4} alkylene, $(CH_2)_rC(O)$, and $(CH_2)_rS(O)_2$;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, 20 benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

25 R^{2b} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

5 A is C₅₋₆ carbocyclic residue substituted with 0-2 R⁴;

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, C(=NR²)NR²R^{2a},
10 NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

15 p, at each occurrence, is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

20 [8] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is *CH(R^a)NHC(O)CH₂;

25 R^a is C(O)C(O)OH;

Z is selected from a CH₂, (CH₂)₂C(O), and CH₂S(O)₂;

A is cyclohexyl or phenyl and is substituted with 0-1 R⁴;

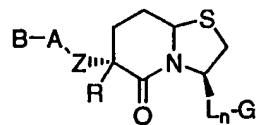
30

R^4 , at each occurrence, is selected from H, =O, OR^2 , CH_2OR^2 , F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ; and,

5 r , at each occurrence, is selected from 0, 1, and 2.

[9] In another even more preferred embodiment, the present invention provides a compound of formula:

10



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$, the * indicates where L_n is bonded to G;

15

R^a is $C(O)C(O)OR^3$;

R is H or NH_2 ;

20 Z is selected from a C_{1-4} alkylene, $(CH_2)_rC(O)$, and $(CH_2)_rS(O)_2$;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

25

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

5 R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

10 A is a C₅₋₆ carbocyclic residue substituted with 0-2 R⁴;

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, 15 and CF₃;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

20 p, at each occurrence, is selected from 0, 1, and 2; and, r, at each occurrence, is selected from 0, 1, 2, and 3.

25 [10] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is *CH(R^a)NHC(O)CH₂;

30 R is H;

R^a is C(O)C(O)OH;

Z is selected from a CH₂, (CH₂)₂C(O), and CH₂S(O)₂;

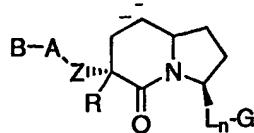
5 A is cyclohexyl or phenyl and is substituted with 0-1 R⁴;

R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR²,
F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

10

r, at each occurrence, is selected from 0, 1, 2, and 3.

[11] In another even more preferred embodiment, the present
15 invention provides a compound of formula:



20 L_n is *CH₂NHC(O)CH₂ or *CH(R^a)NHC(O)CH₂, the * indicates
where L_n is bonded to G;

R is H or NH₂;

R^a is C(O)C(O)OR³;

25

Z is C₁₋₄ alkylene;

R², at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

5 R^{2b}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

10

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is phenyl substituted with 0-2 R⁴;

15

R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

20 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

25 r, at each occurrence, is selected from 0, 1, 2, and 3.

[12] In another still more preferred embodiment, the present invention provides a compound wherein:

30

L_n is *CH(R^a)NHC(O)CH₂;

R is NH₂;

R^a is C(O)C(O)OH;

5

Z is CH₂;

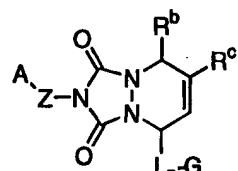
A is phenyl substituted with 0-1 R⁴;

10 R⁴, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃; and,

r, at each occurrence, is selected from 0, 1, and 2.

15

[13] In another even more preferred embodiment, the present invention provides a compound of formula:



20

L_n is *CH₂NHC(O) or *CH(R^a)NHC(O) and the * indicates where L_n is bonded to G;

R^a is selected from C(O)C(O)OR³ and C(O)-A;

25

R^b is selected from H, phenyl, C₁₋₁₀ alkyl, and C₂₋₅ alkenyl;

R^c is selected from H and C₁₋₆ alkyl;

alternatively, R^b and R^c together are -(CH₂)₄-;

5 Z is (CR⁸R⁹)₁₋₄;

R², at each occurrence, is selected from H, CF₃, and C₁₋₆ alkyl;

10 R^{2a}, at each occurrence, is selected from H, CF₃, and C₁₋₆ alkyl;

R^{2b}, at each occurrence, is selected from H, CF₃, and C₁₋₆ alkyl;

15 R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

20 A is selected from:

C₆₋₁₀ aromatic carbocyclic residue substituted with 0-2 R⁴, and

25 5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

5 R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;

R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;

10

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3.

15

[14] In another still more preferred embodiment, the present invention provides a compound wherein:

20 L_n is *CH(R^a)NHC(O) and the * indicates where L_n is bonded to G;

R^a is C(O)C(O)OH or C(O)-(benzothiazol-2-yl);

25 R^b is selected from H, phenyl, C₁₋₁₀ alkyl, and C₂₋₅ alkenyl;

R^c is selected from H and C₁₋₆ alkyl;

alternatively, R^b and R^c together are -(CH₂)₄-;

30 Z is (CR⁸H)₁₋₂;

A is selected from phenyl, naphthyl, and thienyl, and A is substituted with 0-1 R⁴;

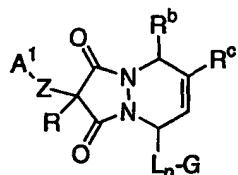
5 R⁴, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

10 R⁸, at each occurrence, is selected from H, methyl and phenyl; and,

15 r, at each occurrence, is selected from 0, 1, and 2.

[15] In another even more preferred embodiment, the present

15 invention provides a compound of formula:



Ln is *CH₂NHC(O) or *CH(R^a)NHC(O) and the * indicates where

Ln is bonded to G;

20

R^a is selected from C(O)C(O)OR³ and C(O)-A;

R^b is selected from H, phenyl, C₁₋₁₀ alkyl, and C₂₋₅ alkenyl;

25 R^c is selected from H and C₁₋₆ alkyl;

alternatively, R^b and R^c together are -(CH₂)₄-;

R is selected from H, benzyl, C₁₋₄ alkyl, and NH₂;

Z is (CR⁸R⁹)₁₋₄;

5 R², at each occurrence, is selected from H, CF₃, and C₁₋₆ alkyl;

R^{2a}, at each occurrence, is selected from H, CF₃, and C₁₋₆ alkyl;

10

R^{2b}, at each occurrence, is selected from H, CF₃, and C₁₋₆ alkyl;

15

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

20 A is selected from:

C₆₋₁₀ aromatic ring substituted with 0-2 R⁴, and 5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

25

R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

5 R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;

R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;

10 p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3.

15 [16] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is *CH(R^a)NHC(O) and the * indicates where L_n is bonded to G;

20

R^a is C(O)C(O)OH or C(O)-(benzothiazol-2-yl);

R^b is selected from H, phenyl, C₁₋₁₀ alkyl, and C₂₋₅ alkenyl;

25 R^c is selected from H and C₁₋₆ alkyl;

alternatively, R^b and R^c together are -(CH₂)₄-;

z is (CR⁸H)₁₋₂;

30

A is selected from phenyl, naphthyl, and thiienyl, and A is substituted with 0-1 R⁴;

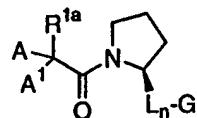
R⁴, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;

10

r, at each occurrence, is selected from 0, 1, and 2.

[17] In another even more preferred embodiment, the present
15 invention provides a compound of formula:



L_n is *CH₂NHC(O) or *CH(R^a)NHC(O) and the * indicates where L_n is bonded to G;

20

R^{1a} is selected from -(CH₂)_r-R^{1b} and NHCH₂R^{1c};

R^{1b} is selected from H, OR², NR²R^{2a}, and NR²SO₂(CH₂)_rR^{2b};

25 R^{1c} is selected from C(O)NR²R^{2a}, S(O)₂R^{2b}, and SO₂NR²R^{2a};

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

5 R^{2b}, at each occurrence, is selected from C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, phenyl substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

10 R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

15 alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

20 R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is phenyl substituted with 0-2 R⁴;

25 A¹ is H or A;

alternatively, A and A¹ and the carbon to which they are attached combine to form fluorene;

30 A² is selected from H, A, and CHA³A⁴;

A^3 is selected from H, A, C_{1-4} alkyl, and $-(CH_2)_rNR^2R^{2a}$;

A^4 is H or A;

5 R^4 , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;

10 R^{4b} , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;

15 R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2;

20 r, at each occurrence, is selected from 0, 1, 2, and 3.

[18] In another still more preferred embodiment, the present invention provides a compound wherein:

25 L_n is $*CH_2NHC(O)$ and the * indicates where L_n is bonded to G;

R^{1a} is selected from $-(CH_2)_r-R^{1b}$ and $NHCH_2R^{1c}$;

R^{1b} is selected from OH, NR^2R^{2a} , and $NR^2SO_2(CH_2)_rR^{2b}$;

30 R^{1c} is selected from $C(O)NR^2R^{2a}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

5 R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

10 R^{2b}, at each occurrence, is selected from C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, phenyl substituted with 0-1 R^{4b}, and pyrrolidinyl substituted with 0-1 R^{4b};

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

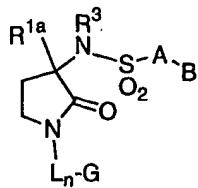
15 alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a piperidine ring substituted with 0-1 R^{4b};

20 R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

25 R^{4b}, at each occurrence, is selected from H, =O, OH, F, Cl, C₁₋₄ alkyl, and NH₂; and,

r, at each occurrence, is selected from 0, 1, and 2.

[19] In another even more preferred embodiment, the present 30 invention provides a compound of formula:



L_n is CH₂;

R^{1a} is -(CH₂)_r-R^{1b};

5

R^{1b} is selected from H, C₁₋₃ alkyl, (CH₂)_rOR², NR²R^{2a}, C(O)R^{2c}, phenyl substituted with 0-2 R⁴, and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

10

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

15

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

20

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

25

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is selected from:

C₆₋₁₀ aromatic ring substituted with 0-2 R⁴, and

5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

5 B is selected from: H, Y, and X-Y

X is selected from C₁₋₄ alkylene, -NR²-, and O;

Y is selected from:

10 C₆₋₁₀ aromatic ring substituted with 0-2 R^{4a}, and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

15 R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

20 R^{4a}, at each occurrence, is selected from H, (CH₂)_rOR², Cl, Br, F, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

25 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

30

[20] In another still more preferred embodiment, the present invention provides a compound wherein:

R^{1a} is -(CH₂)_r-R^{1b};

5

R^{1b} is selected from H, C₁₋₃ alkyl, OH, NR²R^{2a}, and phenyl substituted with 0-2 R⁴;

A is selected from:

10 phenyl substituted with 0-2 R⁴, naphthyl substituted with 0-2 R⁴, thiienyl substituted with 0-2 R⁴, benzothienyl substituted with 0-2 R⁴, 5-aza-benzothienyl substituted with 0-2 R⁴, 6-azabenzothienyl substituted with 0-2 R⁴, and quinolinyl substituted with 0-2 R⁴;

15

B is selected from: H, Y, and X-Y

X is O;

20 Y is phenyl substituted with 0-1 R^{4a};

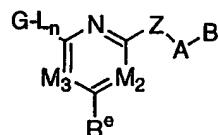
R⁴, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, C(O)NR²R^{2a}, and CF₃;

25

R^{4a}, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, C(O)NR²R^{2a}, and CF₃; and,

30 r, at each occurrence, is selected from 0, 1, and 2.

[21] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is O or S;

M² is N or CR^f;

10 M³ is N or CR^d;

provided that only one of M² and M³ is N;

15 R^e is selected from H, N(CH₃) (CH₂CO₂H) and S-(5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴);

20 R^d is selected from H, F, and Cl;

alternatively, R^d and R^e combine to form -NR³-C(O)-C(R^{1g}R³)-NR³- or -N=CR²-NR³-;

25 R^f is selected from H, F, and Cl;

alternatively, R^e and R^f combine to form -NR³-C(R^{1g}R³)-C(O)-NR³- or -NR³-CR²=N-;

Z is O, provided that Z does not form a N-O or NCH₂O bond with the groups to which Z is attached;

5 R^{1g} is selected from H, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted with A;

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

10 R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

15 R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and 20 phenyl;

A is selected from:

25 C₅₋₆ carbocyclic residue substituted with 0-2 R⁴, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

B is H or Y;

30 Y is selected from:

C₅₋₆ carbocyclic residue substituted with 0-2 R^{4a}, and

5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

5 R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, C(=NR²)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

10 R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR², (CH₂)_r-F, (CH₂)_r-Br, (CH₂)_r-Cl, Cl, Br, F, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, C(=NR²)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃; and,

15

r, at each occurrence, is selected from 0, 1, 2, and 3.

20 [22] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is O;

R^e is N(CH₃) (CH₂CO₂H);

25

R^d is H or F;

alternatively, R^d and R^e combine to form -NR³-C(O)-C(R^{1g}R³)-NR³- or -N=CR²-NR³-;

30

R^f is H or F;

alternatively, R^e and R^f combine to form -NR³-C(R^{1g}R³)-C(O)-NR³- or -NR³-CR²=N-;

5

R^{1g} is selected from H, C₁₋₂ alkyl and benzyl;

A is phenyl substituted with 0-2 R⁴;

10 B is H or Y;

Y is 5 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

15

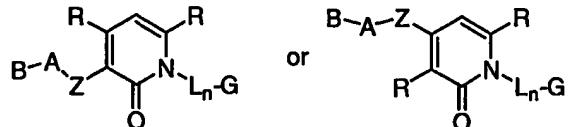
R⁴, at each occurrence, is selected from H, C₁₋₄ alkyl, and NR²R^{2a}; and,

20

R^{4a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and NR²R^{2a}.

[23] In another even more preferred embodiment, the present invention provides a compound of formula:

25



L_n is *CH₂NHC(O)CH₂ or *CH(R^a)NHC(O)CH₂ and the * indicates where L_n is bonded to G;

R^a is C(O)C(O)OR³;

R, at each occurrence, is selected from H, Cl, F, Br, I, OR³, C₁₋₄ alkyl, C(O)NH₂, and NH₂;

5

Z is selected from a C₁₋₄ alkylene and (CH₂)_rSO₂NR³;

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

10

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

15

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

20 A is selected from:

C₅₋₆ carbocyclic residue substituted with 0-2 R⁴, and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

25

B is selected from: H, Y, and X-Y

alternatively, when B is H, A is (phenyl)₂CH- substituted with 0-2 R⁴;

30

X is selected from C₁₋₄ alkylene, -C(O)-, -NR²-, and O;

Y is selected from:

C₅₋₆ carbocyclic residue substituted with 0-2 R^{4a}, and
5-6 membered aromatic heterocyclic system containing
5 from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^{4a};

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F,
10 Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
Cl, Br, F, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃; and,

15 r, at each occurrence, is selected from 0, 1, 2, and 3.

[24] In another still more preferred embodiment, the present
20 invention provides a compound wherein:

L_n is *CH₂NHC(O)CH₂ and the * indicates where L_n is bonded to
G;

25 R, at each occurrence, is selected from H and C₁₋₄ alkyl;

Z is CH₂SO₂NR³;

A is phenyl substituted with 0-2 R⁴;

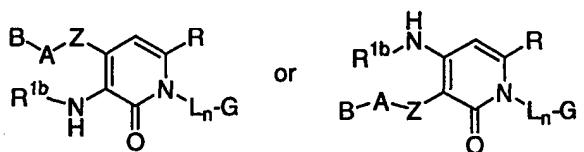
30 B is H;

R^4 , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, and $C(O)NR^2R^{2a}$;
and,

5

r , at each occurrence, is selected from 0, 1, and 2.

[25] In another even more preferred embodiment, the present
10 invention provides a compound of formula:



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$ and the * indicates
where L_n is bonded to G;

15

R^a is $C(O)C(O)OR^3$;

R , at each occurrence, is selected from H, C_{1-4} alkyl, and
NH₂;

20

R^{1g} is H or C_{1-6} alkyl;

Z is selected from a C_{1-4} alkylene and $(CH_2)_rS(O)_p(CH_2)_r$;

25 R^2 , at each occurrence, is selected from H, C_{1-6} alkyl,
benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl,
benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

5 R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

10 C_{3-6} carbocyclic residue substituted with 0-2 R^4 , and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4 ;

B is selected from: H, Y, and X-Y

15 alternatively, when B is H, A is $(phenyl)_2CH-$ substituted with 0-2 R^4 ;

X is selected from C_{1-4} alkylene, $-C(O)-$, $-NR^2-$, and O;

20 Y is selected from:

25 C_{5-6} carbocyclic residue substituted with 0-2 R^{4a} , and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a} ;

alternatively, Z-A-B combine to form $S-C_{1-6}$ alkyl;

30 R^4 , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $-CN$, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

R^{4a} , at each occurrence, is selected from H, =O, $(CH_2)_xOR^2$, Cl, Br, F, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_xNR^2R^{2a}$, $(CH_2)_xC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

5

p is selected from 0, 1, and 2; and,

r , at each occurrence, is selected from 0, 1, 2, and 3.

10

[26] In another still more preferred embodiment, the present invention provides a compound wherein:

15

L_n is $*CH_2NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

R is H or C_{1-4} alkyl;

R^{1g} is H;

20

Z is CH_2 , CH_2S , or $CH_2S(O)_2$;

A is a C_{3-6} carbocyclic residue substituted with 0-2 R^4 ;

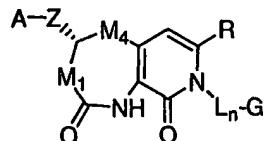
25 B is H

alternatively, Z-A-B combine to form S- C_{1-6} alkyl;

R^4 , at each occurrence, is selected from H, $(CH_2)_xOR^2$, F, Cl, Br, C_{1-4} alkyl, $(CH_2)_xNR^2R^{2a}$, $(CH_2)_xC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ; and,

r, at each occurrence, is selected from 0, 1, and 2.

5 [27] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is *CH₂NHC(O)CH₂ or *CH(R^a)NHC(O)CH₂ and the * indicates
10 where L_n is bonded to G;

M¹ is absent or is selected from CHR, O, and NR²;

M⁴ is selected from NR², CR^t, and C(O);

15 R is selected from H, Cl, F, Br, I, OR³, C₁₋₄ alkyl, OCF₃,
CF₃, and NH₂;

Z is C₁₋₄ alkylene;

20 R², at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl,
25 benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃,
CH₃, benzyl, and phenyl;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is selected from:

5 C₃₋₆ carbocyclic residue substituted with 0-2 R⁴, and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

10 R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

15

[28] In another still more preferred embodiment, the present invention provides a compound wherein:

20 L_n is *CH₂NHC(O)CH₂ and the * indicates where L_n is bonded to G;

M¹ is absent;

25 R is selected from H and C₁₋₄ alkyl;

Z is CH₂;

A is C₃₋₆ carbocyclic residue substituted with 0-1 R⁴;

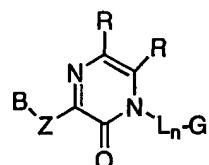
30

R^4 , at each occurrence, is selected from H, C₁₋₄ alkyl,
 $(CH_2)_rNR^2R^{2a}$, and CF₃; and,

r , at each occurrence, is selected from 0, 1, and 2.

5

[29] In another even more preferred embodiment, the present invention provides a compound of formula:



10

L_n is *CH₂NHC(O)CH₂ or *CH(R^a)NHC(O)CH₂ and the * indicates where L_n is bonded to G;

15

R^a is C(O)C(O)OR³;

R , at each occurrence, is selected from H, Cl, F, Br, I,
 OR^3 , C₁₋₄ alkyl, C(O)NH₂, and NH₂;

20

Z is (CHR⁸)NR³, (CHR⁸)₂NR³, and (CHR⁸)₂SO₂R³;

25

provided that when Z is (CHR⁸)₂NR³, then B is absent;

R^2 , at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

5 R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a} , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

10 B is H or Y;

Y is selected from:

15 C_{5-6} carbocyclic residue substituted with 0-2 R^{4a} , and 5-6 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a} ;

20 R^{4a} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, Cl, Br, F, I, C_{1-4} alkyl, -CN, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

25 R^8 , at each occurrence, is selected from H, C_{1-6} alkyl and phenyl; and,

30 r, at each occurrence, is selected from 0, 1, 2, and 3.

[30] In another still more preferred embodiment, the present invention provides a compound wherein: